Original Article

# Intravenous lidocaine bolus for reducing nefopam-induced venous pain: A randomized, intrasubject comparison trial

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## Abstract

**Background and Aims:** Intravenous nefopam reduces postoperative pain and opioid consumption but can cause infusion-related pain. We aimed to investigate whether lidocaine can effectively reduce this pain.

**Material and Methods:** This prospective, randomized, double-blind, controlled, intrasubject comparison trial included 42 patients (20–60 years) undergoing elective surgery under regional or peripheral anesthesia. In the postanesthesia care unit, two 50 mL syringes containing nefopam (20 mg) diluted in saline (100 mL) were sequentially infused in 15 min into venous catheters in the left and right arms. Patients were randomly assigned to the "left side" or "right side" group based on the arm in which a bolus of 1% lidocaine (2 mL) (study group) was administered before nefopam infusion. Normal saline (2 mL) was administered on the control side. Numerical Rating Scale scores and the incidence of pain (scores > 3) and nausea or vomiting were recorded at 1, 5, 10, and 15 min.

**Results:** The analysis included 42 patients (84 infusions). Compared with the placebo, lidocaine lowered the mean infusion-related pain at 1 (0.07 vs. 2.21, $P < 0.001$), 5 (2 vs. 4.21, $P < 0.001$), 10 (2.02 vs. 3.95, $P < 0.001$), and 15 min (1.62 vs. 3.16, $P = 0.003$). At 5 min, significantly higher percentages of infusion sites with moderate and higher pain scores (> 3) were observed on the control side (30.95% vs. 14.29%, $P = 0.000$). Seven patients exhibited nausea or vomiting (16.7%).

**Conclusion:** For the nefopam infusion rate and concentration that we used, a 20 mg lidocaine pretreatment bolus significantly reduces infusion-related pain.

**Keywords:** Analgesic, anesthesia, intravenous infusion, nefopam, postoperative pain

## Introduction

According to the Enhanced Recovery After Surgery (ERAS) protocol, multimodal analgesia is the gold standard in the treatment of postoperative pain as more than one modality of pain control aids in achieving effective analgesia while reducing opioid-related side effects.[1-3] Nevertheless, currently, there is no consensus regarding the best approach to multimodal analgesia, and many treatment modalities have been suggested.[4] Among these, nefopam, a non-opioid, non-steroidal drug, has emerged as a good candidate for use in multimodal analgesia.[5,6]

Nefopam is a nonopioid and nonsteroidal analgesic medication that is derived from a non-sedative benzoxazocine. Nefopam does not exhibit anti-inflammatory effects and does not bind to opioid receptors.[7,8] Nefopam infusion can reduce nociceptive pain by decreasing the reuptake of serotonin, norepinephrine, and dopamine.[9] It also affects the glutaminergic pathway by the modulation of calcium and sodium channels.[10] Nefopam

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in combination with various analgesic drugs, such as opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and paracetamol, has provided good analgesia in most preclinical and clinical studies involving surgery.[5,11-13] There are many studies on the effectiveness of nefopam on various types of procedures such as orthopedic surgery, spine surgery, laparoscopic surgery, and gynecological surgery with a more current note on neuropathic pain.[9,14-16]

Despite being an analgesic medication, nefopam induces pain during intravenous infusion. Kim *et al*.[17] found that the incidence of infusion-related pain varied from 86.2%–100%, depending on the infusion rate and concentration of the injectate. Many patients also complained about feeling an unpleasant sensation along the arm in which the drug is infused. Lidocaine can be administered to prevent medication-induced pain and is used in the induction of anesthesia with propofol.[18] Therefore, the aim of this double-blinded, randomized, controlled study was to ascertain the efficacy of a preinfusion bolus of lidocaine in easing nefopam-induced arm pain.

## Material and Methods

The study was approved by the Instutional Review Board, Faculty of Medicine Chulalongkorn University (COA No. 379/2020, IRB No. 661/62), and was registered with Thai Clinical Trials Registry: TCTR20201125006. Written informed consent was obtained from the study participants. A total of 42 patients scheduled for elective surgery under regional anesthesia (neuraxial or peripheral anesthesia) from March to October 2020 were included in this double-blinded, randomized, intrasubject comparison study. Our trial was done following the CONSORT 2010 guidelines.

The inclusion criteria were patients aged between 20 and 80 years and who were scheduled for elective surgery under regional or peripheral anesthesia without sedation. The exclusion criteria included patients allergic to any of the medications used in the study, or who could not understand the procedures or assign a pain score, or who were previously exposed to intravenous nefopam, or who were receiving any medication that could inhibit the reuptake of serotonin at the time.

After the eligible patients signed the informed consent form, each patient was advised how to rate their pain with scores ranging from 0 to 10 on the Numerical Rating Scale (NRS), with 0 = pain-free and 10 = the worst pain imaginable.[19] During surgery, all patients were cannulated in one arm for surgical reasons. Ten minutes after the surgery, the other arm was also cannulated with another 22-G venous catheter.

The patients were randomized with the block randomization technique into the "left side" or "right side" group. In the left-side group, 2 mL of 1% lidocaine solution (study group) was injected into the venous catheter immediately before the infusion of nefopam. On the contralateral side, an injection of 2 mL of normal saline (placebo-control) was injected before the infusion of nefopam. The bolus solutions were pre-prepared and administered by a postanesthesia care unit (PACU) nurse. Nefopam (Pharmasynthese, Elbeuf, France) (10 mg) was diluted in 50 mL of normal saline. The assessor and patients were blinded to the solutions administered. Immediately after the bolus of lidocaine or saline solution was administered, nefopam was infused at a rate of 50 mL/15 min into each arm of the participants. All infusions were administered first into the left arm, followed by the right arm. The total infusion time in both arms was 30 min [Figure 1]. The procedures were carefully carried out in accordance with the Helsinki Declaration of 1975, as revised in 1983.

At 1, 5, 10, and 15 min during each infusion, the patients were asked to rate the pain in the arm in which nefopam was being infused using the NRS. The occurrence of nausea and vomiting was also recorded as "positive" or "positive with treatment needed."

### Statistical analysis

We hypothesized that 30% of the patients who were administered nefopam would have an NRS score

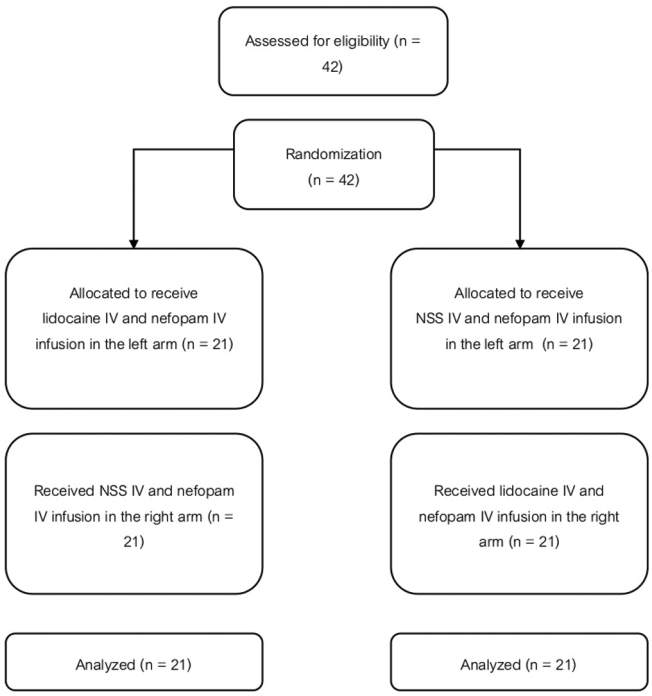


**Figure 1:** Flowchart depicting the group allocation and treatment of the participants. NSS: normal saline solution

of >3,[17] (proportion at pre-treatment (p10) = 0.300) and that 5% of those who were administered lidocaine would have an NRS score of > 3 (proportion at post-treatment (p01) = 0.05). For a desired power of 0.8 and an alpha level of 0.05, we used a mixed model analysis to calculate the sample size needed to identify the mean difference in the pain scores between the groups at the 1-, 5-, 10-, and 15-min time points, with the score at 5 min being the primary outcome. McNemar's paired proportion test was used to test the difference in the percentage of patients with NRS >3 between each arm at the 1-, 5-, 10-, and 15-min time points. SPSS version 20.0 (IBM Corp. Released 2011, IBM SPSS Statistics for Windows, Armonk, NY, USA) was used for all the analyses. A *P* value of less than 0.05 was considered statistically significant.

## Results

A total of 42 patients were enrolled, and none dropped out. These 42 patients were divided into two groups, and all were included in the analysis (left arm = 42, right arm = 42). The patient demographic and clinical characteristics including, sex, age, weight, height, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, type of anesthesia, duration of surgery, and type of intraoperative intravenous catheter are presented in Table 1.

All patients were randomized to receive lidocaine in one of their arms. The nefopam infusion was delivered first into the left arm in all the patients, in whom 21 (50%) received lidocaine pre-treatment. Pre-treatment with lidocaine resulted in a statistically significant lower pain score at all the time points, compared to saline, regardless of whether the left or right arm was being assessed. The analysis was thus performed without including the infusion site/side as a factor. At the 1-, 5-, 10-, and 15-min time points, mean numerical pain scores of 0.07, 2.0, 2.02, and 1.62 were recorded on the lidocaine side compared to 2.21, 4.21, 3.95, and 3.17 on the control side. The 95% confidence intervals were − 2.18, −2.21, −1.93, and − 1.55, which were in favor of the lidocaine bolus. All the *P* values were less than 0.005 [Table 2]. Our primary outcome was the numerical pain score 5 min after the infusion, and the mean (and standard error of the mean) pain scores were 2 (0.35) and 4.21 (0.42) in lidocaine and control sides, respectively (*P*-value <0.001) [Table 2].

A significantly higher percentage of patients experienced pain levels with scores of ≤3 at the infusion site on the lidocaine

**Table 1: Demographic data**

| Characteristics | Data |
|---|---|
| Gender, Male; *n* (%) | 34 (81.0) |
| Age, year; mean±SD | 54.07±15.82 |
| Weight, kg; mean±SD | 65.62±11.97 |
| Height, cm; mean±SD | 165.75±7.15 |
| BMI, kg/m$^2$; mean±SD | 23.83±3.62 |
| ASA; *n* (%) | |
| I | 15 (35.7) |
| II | 27 (64.3) |
| Type of anaesthesia; *n* (%) | |
| SAB | 41 (97.6) |
| PNB | 1 (2.4) |
| Duration of surgery, min; mean±SD | 52.24±26.41 |
| Lidocaine injection side, right; *n* (%) | 21 (50) |
| Catheter site; *n* (%) | |
| Hands | 41 (97.6) |
| Forearms | 1 (2.4) |
| Catheter size; *n* (%) | |
| 20G | 20 (47.6) |
| 22G | 22 (52.4) |
| N/V; *n* (%) | 7 (16.7) |

*Abbreviations: SD, standard deviation; BMI body mass index; ASA, American society of Anesthesiologists status; SAB, Subarachnoid block; PNB, peripheral nerve block*

**Table 2: Pain score at the 1-,5-,10-, and 15-minute timepoints post infusion with and without lidocaine bolus**

| | With lidocaine Mean±SE. | Without lidocaine Mean±SE. | Mean difference (95%CI) | *P* |
|---|---|---|---|---|
| 1 min | 0.07±0.05 | 2.21±0.43 | -2.14 (-2.98, -1.31) | <0.001* |
| 5 min | 2±0.35 | 4.21±0.42 | -2.21 (-3.28, -1.14) | <0.001* |
| 10 min | 2.02±0.35 | 3.95±0.4 | -1.93 (-2.96, -0.89) | <0.001* |
| 15 min | 1.62±0.32 | 3.17±0.41 | -1.55 (-2.55, -0.54) | 0.003* |

*Mixed model analysis. (grouping variable: with lidocaine and without lidocaine)*P value<0.05, Abbreviations: CI=confidence interval; SE=standard error of the mean*

**Table 3: Percentage of patient with pain score of ≤3 or of >3 at the infusion sites with lidocaine and without lidocaine at the 1-,5-,10-, and 15-minute timepoints**

| | Pain score at infusion sites (*n*=84) | | *P* |
|---|---|---|---|
| | NRS ≤3; *n* (%) | NRS >3; *n* (%) | |
| At 1 min | | | |
| With lidocaine | 42 (100) | 0 (0) | 0.000* |
| Without lidocaine | 30 (71.43) | 12 (28.57) | |
| At 5 min | | | |
| With lidocaine | 36 (85.71) | 6 (14.29) | 0.000* |
| Without lidocaine | 13 (30.95) | 29 (69.05) | |
| At 10 min | | | |
| With lidocaine | 34 (80.95) | 8 (19.05) | 0.000† |
| Without lidocaine | 16 (38.10) | 26 (61.90) | |
| At 15 min | | | |
| With lidocaine | 34 (80.95) | 8 (19.05) | 0.022† |
| Without lidocaine | 25 (59.52) | 17 (40.48) | |

**McNemar's test of paired proportions NRS >3. †Binomial distribution used. (*) P<0.05. Abbreviations: NRS, numerical rating scale score*

side at all the time points, as shown in Table 3. Furthermore, 85% (n = 36) of the infusion sites on the lidocaine side had pain scores of ≤3 compared with 30.95% (13) on the control side (*P*-value = 0.000) [Table 3]. Among all the patients, 16.7% exhibited nausea and vomiting (n = 7) without the need for treatment.

## Discussion

As an analgesic medication, nefopam is a promising candidate that could be used in multimodal pain management modalities. Unfortunately, it causes several side effects, such as palpitation, sweating, hypertension, blurred vision, and pain at the infusion site.[17,20] To prevent these undesirable effects, clinicians are advised to infuse the medication slowly over 15 min.[21] Pain at the injection site can range from mild/irritating to severe/excruciating, and many patients ask for the medication to be discontinued during administration. This condition can cause anxiety, sleep disturbance, and reduced patient satisfaction.[22] In the current literature, there are a very limited number of reports on the level and incidence of nefopam-induced pain and on how this venous pain could be mitigated. This venous pain can mask the effects of surgical or acute pain treatment and, hence, leads to many clinicians feeling reluctant to use nefopam.[17]

The rate of infusion and concentration of the infused solution might play a role in the development of pain. Kim *et al*.[17] have suggested that slowing the infusion rate could decrease the level of pain from severe to mild-moderate. Despite their attempt to reduce the pain by lowering the infusion rate to 60 mL/h (20 min per infusion), which is already slower than the manufacturers' advised rate, 20% of their patients still reported experiencing moderate pain (defined as a visual analog score of 4'7). In our study, all the patients reported a mean NRS score of less than 2 in the arm administered lidocaine at the pretreatment stage. Similar to Kim *et al*.'s[17] finding indicating that 77% of the patients experienced moderate pain at an infusion rate of 120 mL/h, our results revealed that 69% of the patients experienced moderate pain at 200 mL/h.

The recommended dosage for analgesia from pharmaceutical company was a single infusion of 20 mg diluted to 100 mL with normal saline, which was the mean effective dose (ED50) of nefopam.[23] This was why we used 10 mg of nefopam in 50 mL of normal saline on each arm which was equivalent to 20 mg, whereas the previous study used 30 mg in 20 mL of normal saline.[17] This might be another reason that explains why our pain score was lower than that in the previous study.

Currently, there is no study on the use of any pretreatment medication for alleviating the venous pain caused by nefopam. Lidocaine is a commonly used local anesthetic that acts locally and systemically. Intravenous lidocaine can reduce several types of pain, including cancer-related pain, neuropathic pain, postsurgical pain, refractory pain syndrome-related pain, and propofol infusion–induced pain.[18,24-27] In many studies on propofol-induced venous pain, several dosages of lidocaine were used and reduced the injection-related pain caused by propofol. However, in a systematic review on lidocaine use and propofol-induced pain conducted by Euasobhon, it was suggested that 20 mg of lidocaine is sufficient to reduce the pain,[18] which is why we chose to administer a bolus of 2 mL of 1% lidocaine.

Nonetheless, the mechanism by which lidocaine eases the pain caused by the injection of these medications remains unknown. A study by Xing *et al*. indicated that lidocaine can block peripheral and central voltage-gated sodium channels in the dorsal root ganglion.[27] However, at the dosage administered in this study, the peripheral mechanism is more likely.

### Limitations

We did not record cardiovascular effects even though all the patients complied with the standard postanesthesia monitoring protocol because our study was conducted immediately after surgery. Therefore, the heart rate and blood pressure changes may not have been a result of the side effects of nefopam. Consequently, there might have been a major confounding factor resulting from the surgical or anesthetic techniques.

Only one dosage of lidocaine (20 mg) was used in our study. The study by Xing *et al*.[27] indicated that 40 mg is a better dosage for alleviating propofol-induced venous pain. If we had used a higher dosage, the improvement in pain might have been more pronounced, and the effects of lidocaine might have been a combination of both peripheral and central mechanisms.

We realize that, currently, there are no guidelines or consensus regarding the infusion rate and optimal concentration of nefopam in multimodal analgesia. Further studies should be focused on investigating whether pretreatment with lidocaine can be used with other techniques of administering nefopam, or whether mixing lidocaine with nefopam could result in the same effect that we observed in this study.

## Conclusion

For the infusion rate and concentration of nefopam that we used, a pre-treatment bolus of 20 mg of lidocaine significantly reduced the pain resulting from the infusion.

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## Conflicts of interest

In 2019, Dr. Marvin was a speaker for DKSH, a distributor for nefopam in Thailand.

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